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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/259,389	02/26/99	GEORGOPOULOS K	10287/043001

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EXAMINER	
WOITACH, J	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

File

Office Action Summary	Application No. 09/259,389	Applicant(s) Georgopoulos et al.
	Examiner Joseph Woitach	Group Art Unit 1632

☒ Responsive to communication(s) filed on *Oct 10, 2000*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-17* is/are pending in the application.

Of the above, claim(s) *6-9, 12, 14, and 17* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-5, 10, 11, 13, 15, and 16* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *7*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Applicants amendment filed October 10, 2000, Paper No. 8, has been entered. Claims 1-17 are pending. Claims 3-5, 10, 11 and 15 have been amended. Claim 6-9, 12, 14 and 17 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 1-5, 10, 11, 13, 15, 16 are pending and are under current examination.

Claim Objections

Claim 11 objected to under 37 CFR 1.75(c) as being in improper form is withdrawn. Applicants amendment has obviated the objection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15 and 16 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled

in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants argue that compelling evidence involving the Ikaros gene, a gene related to Helios as a member of the Ikaros gene family, 'provides sufficient guidance to enable a skilled artisan to treat disorders characterizes by misexpression of Helios' (applicants amendment page 4; last paragraph). Further, Applicants argue that Examiners characterization of gene therapy is not dismal and that gene transfer is feasible as demonstrated by human trials discussed in Crystal *et al.* (page 6; first two paragraphs). Applicants arguments have been fully considered but not found persuasive.

As summarized in the previous office action, the application is silent with respect to the role of Helios in any disorder or any examples that point to any specific function of Helios. Sequence homology demonstrates that Helios is a member of the T cell-restricted Ikaros family and experiments show that Helios can interact with the other family members. Examiner agrees with Applicants summary of the Ikaros gene and that the absence of Ikaros can lead to development disorders, however, this does not clearly support a role for the Helios gene in these functions. Similar experiments have not been done for Helios and so no examples for a function of Helios exist. Further, the expression pattern in different tissues and co-localization of the protein is different from that of Ikaros suggesting a different role for the Helios gene product. Further, Hahm *et al.* point out that even though work to elucidate the role of Ikaros has been done, 'the specific functions of Helios and of the Helios-Ikaros complex remain unknown' and

'remain to be elucidated' (page 792; discussion). While deletion or mutations of Helios may produce similar effects seen for that of Ikaros, empirical experiments must be done to demonstrate this fact.

Since Helios is a member of a larger family of genes, one may suggest a role or function based on family member similarity, however, the expression pattern of the family members differ. Kelly *et al.* state that '[w]hereas Ikaros and Aiolos are predominantly expressed in hematopoietic sites, Helios is also expressed elsewhere' (page 514; last paragraph). Different tissue distribution and co-localization of the proteins suggests a different role for the Helios gene product than that of the other family members. While the role of Helios may be important in hematopoietic development, without the detailed experiments performed like those of other Ikaros family members, one can not predict the role or function of Helios. Finally, Kelly *et al.* state [m]utational analysis of the Helios gene will help to dissect its role in regulating progenitor development in the hematopoietic system' (page 514; final paragraph), suggesting the function of Helios is not known, and that one can not relate changes in Helios expression or mutations of the gene to any sort of risk towards any disorder.

With respect to the characterization of gene therapy, Examiner agrees that current gene transfer protocols show promise, however gene transfer *per se* is not the basis of the rejection. As pointed out in the previous office action, even if the function of Helios was known, or what disease is associated with a particular expression of Helios, the *in vivo* or *ex vivo* gene therapy methods to deliver the DNA or corresponding peptide would involve undue experimentation.

Verma *et al.* and Anderson summarizes the state of gene therapy for several clinical trials and conclude that major deficiencies still exist including poor delivery system, both viral and non-viral, and poor gene expression after genes are delivered. The instant specification is silent to what diseases result from the misexpression of Helios, and there is no guidance nor example indicating the effect of increased or decreased expression of Helios giving rise to any phenotype or disease, and therefore one of skill in the art would not know how to make the appropriate vectors for expression or how to use said vectors. The basis of the rejection is not if gene transfer is possible, it is that if the instant specification provides the necessary guidance to perform the gene transfer protocols. Since the instant specification does not teach any disease which is associated with the misexpression of Helios, and there is no guidance nor examples of phenotypes which result from the misexpression of Helios as are available for other Ikaros family members, one of skill in the art would not know how to perform gene therapy protocols. Further, as summarized in Verma *et al.* and Anderson, many gene therapy protocols are unsuccessful because of the inability to obtain the proper expression of the transferred gene, and because the instant application relies on the vectors and protocols of others taught in the art, applicants face the same shortcomings of the current protocols. Even if a disease were associated with the misexpression of Helios, the instant specification does not provide the guidance or examples to demonstrate that the proper levels of Helios can be obtained by current protocols.

Therefore, in view of the of the lack of guidance, working examples, breadth of the claims, skill in the art and state of the art at the time of the claimed invention, it would require undue

experimentation by one of skill to practice the invention as claimed. For the reasons above and of record the rejection is maintained.

Claims 1, 3-5,10, 11, 13 and 15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 encompasses a nucleic acid sequence which is at least 60% identical to SEQ ID NO: 1, 3, or 5. SEQ ID NO: 1 is a polynucleotide sequence which encodes Helios, and SEQ ID NOs: 3 and 5 represent splice variants identified by RT-PCR. Dependant claims 3-5 encompass a nucleic acid which hybridizes to SEQ ID NO: 1, 3, or 5, encodes protein which reacts with an antibody specific for the amino acid sequence encoded by SEQ ID NO: 1, 3, or 5 and any fragment of at least 60 amino acids in length. The inventions comprise the genuses of Helios gene and fragments thereof. These genuses would appear to include sequences which encode functional Helios proteins. They may include fragments of Helios, and other variants comprising deletions, substitutions, insertions, additions, or replacements of Helios sequences. Since there is no language describing functional limitations of the claimed sequences, the claimed nucleic acid sequences also include sequences which do not encode a functional Helios protein. The genus also conventionally includes genomic clones of the genes encoding these polypeptides, comprising introns and natural promoters since these would also hybridize to SEQ ID NO: 1, 3 or 5.

Applicant is referred to the interim guidelines on written description published December 21, 1999 in the Federal Register, Volume 64 Number 244, pp. 71427-71440 (also available at www.uspto.gov). The following passage is particularly relevant.

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.
>
> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within a genus, one must describe a sufficient number of species to reflect the variation within the genus. What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus.

The instant specification appears to disclose three polynucleotide sequences encoding a Helios protein, SEQ ID NO: 1, 3, and 5. No genomic clones or sequence variants which encode biologically active proteins are described by complete structure. The only relevant identifying characteristic disclosed in the specification is that the sequences must encode proteins having appropriate biological activity. However, no correlation has been disclosed between any 60% identical sequence and any protein structure which is sufficient for biological activity. The specification only describes sequences which have an appropriate biological function of Helios as as a transcription factor, which funcitons in concert with other polypeptides which are part of the Ikaros gene family. The specification does ot describe sequences which have this biological function for any sequence 60% identical to SEQ ID NO: 1, 3, or 5. Because the specification fails to describe more than a single species of each genus, and because one of skill in the art could not

be expected to predict the biological activity of the sequence variants encompassed by the claims, the written description requirement has not been met. The specification provides a written description only for Helios which is encoded by nucleic acids set forth in SEQ ID NO: 1, 3, or 5.

Claims 1-5, 10 11 and 13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 1 encompasses a nucleic acid sequence which is at least 60% identical to SEQ ID NO: 1, 3, or 5. Dependant claims 2-5 encompass the specific nucleic acid sequences set forth in SEQ ID NO: 1, 3 or 5, a nucleic acid which hybridizes to SEQ ID NO: 1, 3, or 5, encodes protein which reacts with an antibody specific for the amino acid sequence encoded by SEQ ID NO: 1, 3, or 5, and any fragment of at least 60 amino acids in length. The specification provides adequate guidance for making SEQ ID NO: 1, 3 and 5 and use of these to make the encoded protein, and provides adequate teaching on how to make and use other nucleic acid sequences which encode a protein with a similar sequence, however the specification fails to provide guidance on use of the nucleic acid sequences. Further, as discussed above in the written description rejection, no guidance is given for making or using the nucleic acid sequences which meet the hybridization limitations, or react with an antibody, or fragments thereof.

As set forth in *In re Fisher,* 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

In *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991), the court ruled that a claim to a large genus of possible genetic sequences encoding a protein with a particular function that needs to be determined subsequent to the construction of the genetic sequences may not find sufficient support under 35 USC 112, 1st paragraph, if only a few of the sequences that meet the functional limitations of the claim are disclosed and if undue experimentation would be required of one skilled in the art for determining other genetic sequences embraced by the claim. In the instant case there are a large number of nucleic acid sequences which contain 'at least about 60 amino acids' and share enough homology to hybridize to the recited SEQ ID NOs, however these sequences encode various unrelated proteins. Therefore, while the specification provides the necessary guidance to make the polynucleotides Set forth in SEQ ID NO: 1, 3 or 5, it does not provide the necessary guidance for one of skill in the art to use the nucleic acid sequences which do not encode a Helios protein. Further, since no functional language is associated with the Helios protein encoded by SEQ ID NO: 1, 3 or 5, one

of ordinary skill in the art would not know how to use these defined sequences except in further characterization of the sequences themselves.

In view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time the invention was made, it would have required one of skill in the art undue experimentation to practice the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5, 10 and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

Claim 1 is vague and unclear in the recitation of 'which is 60% identical to SEQ ID NO: 1, 3, or 5' because the metes and bounds of identical are not clearly defined. It is unclear if identity is over the full length of the sequence or if a sequence which is truncated by 40% of its sequence or deleted of 40% of its internal sequence would still be considered 60% identical. When read in light of the specification identity is the equivalent to homology (page 31; lines 4-14), though an example is provided, it is not clear if this example excludes deletions and truncations encompassed by the claim as written.

Claim 3 is vague and indefinite in the recitation of "under high stringency conditions" because the conditions are not specifically described in the specification or the claim, so the metes and bounds have not been adequately defined. Though the instant specification has been amended to recite hybridization conditions cited in *Current Protocols in Molecular Biology*, these conditions are only examples as recited in the incorporated text (applicants amendment paper number 8; page 1, third line-entered on page 56; line 30). Since these are only examples, the specific conditions for stringent hybridization are still not adequately defined. Dependent claims are included in the rejection because they fail to clarify the basis of the rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> a person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-5 rejected under 35 U.S.C. 102(a) as being anticipated by Hahm *et al.* is withdrawn.

Applicants declaration filed under 37 CFR 1.131 establishing a date of invention prior to February 4, 1998, before the Hahm *et al.* publication date overcomes this rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) a patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5, 10, 11 and 13 rejected under 35 U.S.C. 103(a) as being unpatentable over Hahm *et al.* in view of Molnar *et al.* is withdrawn.

Applicants declaration filed under 37 CFR 1.131 establishing a date of invention prior to February 4, 1998, before the Hahm *et al.* publication date overcomes this rejection.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach, whose telephone number is (703) 305-3732. The examiner can normally be reached on Monday through Friday from 8:00 to 4:30 (Eastern time).

If attempts to reach the examine by telephone are unsuccessful, the examiner's supervisor, Karen M. Hauda, can be reached on (703) 305-6608. The fax number for group 1600 is (703)308-4724.

An inquiry of a general nature or relating to the status of the application should be directed to Kay Pickney whose telephone number is (703) 305-3553.

Joseph T. Woitach

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